Clinical Case of Surreptitious Hypoglycemia Due to Deliberate Insulin Analog Administration

Marina Yukina, Nurana Nuralieva, Ekaterina Troshina, Natalya Malysheva, Zamira Zuraeva and Alina Bratchikova

Endocrinology Research Centre, Moscow, Russia.

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ABSTRACT: Hypoglycemic syndrome is a life-threatening condition that can lead to hypoglycemic coma and death. Surreptitious hypoglycemic syndrome is the deliberate use of insulin preparations or oral hypoglycemic drugs aimed to reduce blood glucose level. If human insulin is injected, high level of immunoreactive insulin (IRI) and low level of C-peptide at the moment of hypoglycemia are always detected. However, the fact of deliberate administration of insulin analogs is difficult to prove. In these cases if insulin kit test with low cross-reactivity with insulin analogs is used, the low levels of IRI and C-peptide will be suspected. Some experts suggest the presence of cross reactivity with analogs of insulin in a number of commercial kits, which makes it possible to detect cases of surreptitious hypoglycemia. We present a clinical case of a patient with surreptitious hypoglycemia due to the administration of insulin analogs and discuss the problems of its laboratory diagnosis.

KEYWORDS: Hypoglycemic syndrome, surreptitious hypoglycemia, insulin analog administration, Munchausen syndrome

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CORRESPONDING AUTHOR: Yukina MYu, Endocrinology Research Centre, Dm. Ulyanova Street, 11, Moscow 117036, Russia. Email: kuronova@yandex.ru

Introduction

Surreptitious hypoglycemic syndrome (HGS) is the deliberate use of insulin preparations or oral hypoglycemic drugs to reduce blood glucose level.[1] This condition has been described in patients without disorders of carbohydrate metabolism and in patients with diabetes mellitus (DM) as well.[2-4] Patients may often present with psychiatric diseases and psychosocial problems.[2,5,6] Moreover, surreptitious hypoglycemia is common in relatives of patients with DM.[7] Surreptitious hypoglycemia is one of the possible types of the Munchausen syndrome. The term Munchausen syndrome is used in relation to patients who chronically fabricates signs or symptoms of a disease.[8] Surreptitious pathologies are characterized by variability of symptoms during therapy, multiple hospitalizations, and different specialists' check-ups. Unexplained long remission from hypoglycemia episodes with further resumption is often observed.[9]

During laboratory research, exogenous injection of human insulin is characterized by high levels of this hormone, as well as suppression of C-peptide and proinsulin.[10] However, in cases of surreptitious injection of insulin analogs, many authors[2,11-13] reported the low level of detected insulin. Some experts have linked these cases to low cross-reactivity of several types of immunoassay with insulin analogs.[2,11,12,14-17] This is due to differences in immunoreactivity of insulin analogs and human insulin because of amino acid sequence changing in the C-terminal part of the B-chain.[11] Moreover, changing of only 1 amino acid can highly decrease the ability of some analyzers to observe this preparation.[17]

Manufacturers often do not mention low cross-reactivity of immunoassay kits with several insulin analogs, which causes problems for clinicians and laboratorians to interpret analysis, if the surreptitious hypoglycemia is suspected.[17] Considering the above, a number of scientists conducted research to find out the specificity of different kits in insulin preparations detection.[17-19] In particular, Parfitt et al[17] compared 10 analytical platforms, including mass-spectrometer immune analysis (MSIA), relating to the detection of 15 insulin preparations (Table 1, adapted by the authors: only human insulin and insulin analogs are mentioned). As presented in the table, human regular insulin, which has amino acid sequence identical to endogenous insulin, is easily detected by all analyzers, in contrast to insulin analogs.[17]

In Russia, surreptitious hypoglycemia tends to be a diagnosis of exclusion.[20] To prove the exogenous administration of hypoglycemic drugs a provocative fasting test is carried out under round-the-clock observation and complete isolation of the patient from contact with medications (in intensive care unit, for example), that significantly increases the cost of examination.

We present the clinical case of surreptitious hypoglycemia due to insulin analog administration. To the best of our knowledge, this is the first case proven by immune analysis with high cross-responsiveness to this group of drugs in Russia. The patient gave written informed consent to the publication of this article.

Clinical case

Patient A., 34 years old, was admitted to the Endocrinology Research Centre (ERC) in July 2020 with complaints of episodes of blurred consciousness and significant hunger that occur several times a week at any time of the day, except for the period of sleep, associated with a decrease in glycaemia to 1.4 mmol/l, and are stopped by the administration of glucose solution or a sweet meal. Also, the patient complained of

Table 1. Cross-Reactivity (%) of Different Kits with Insulin Preparations (Low Level: <20%; Medium Level: 20%-79%; High Level: >80%; C: Correct Identification of An Insulin Analog Using the MSIA Analyzer During Qualitative Determination).[17]

KITS	HUMAN INSULIN			INSULIN ANALOGS					
				1 AMINO ACID DIFFERENCE	2 AMINO ACID DIFFERENCE		3 AMINO ACID DIFFERENCE	COMPLEX[a] INSULINS	
	ACTRAPID	HUMULIN S	HUMULIN I	ASPART	LISPRO	GLULISINE	GLARGINE	DETEMIR	DEGLUDEC
Mercodia Iso-Insulin	140	140	140	140	139	140	93	46	44
Abbott Architect	108	124	115	110	129	10	140	30	24
Mercodia Insulin	95	113	113	0	0	0	7	0	0
Roche Elecsys Insulin	107	134	123	0	0	0	20	0	4
MSIA	140	140	139	C	C	C	C	C	C

Adapted by the authors (only human insulin and insulin analogs are mentioned).
[a]Having fatty acid residues in their structure.

Table 2. The Patient's Laboratory Data During Spontaneous Hypoglycemic Episode (At the Local Facility).

TEST	VALUE (UNITS)	REFERENCE INTERVAL
Glucose	2 mmol/l	3.1-6.1
Insulin (RE)	0.483 μU/ml	2.3-26.4
C-peptide	0.486 ng/ml	1.1-4.4
Proinsulin	0.7 pmol/l	0.7-4.3
TSH	1.651 mUI/ml	0.25-3.5

constant weakness, sleepiness, anxiety, increased sweating, chilly extremities, ejaculatory function disorder.

According to the medical history of the patient, the episodes of decreasing the glycaemia level as low as 3 mmol/l were repeatedly recorded for the first time during medical check-up for compulsory military service in 2002 to 2003. Consequently, the patient was deemed unfit for military service (medical reports were not provided). Hypoglycemia had not occurred until 2008, when patient again started to notice regular deterioration in well-being associated with a decrease in glucose levels to a minimum of 2.5 mmol/l. The patient remembered that at the moment of hypoglycemia the insulin level was elevated. In addition, doctors of the local facility performed multislice computed tomography (MSCT) of the pancreas, which did not reveal any pathology and therefore, "idiopathic hyperinsulinism" was diagnosed. The endocrinologist recommended regular intake of slowly digestible carbohydrates and the elimination of rapidly digestible carbohydrates. After nutritional correction, attacks became less frequent. Deterioration of health was reported in July 2018, when, against the background of short-term physical activity and weight loss, episodes of loss of consciousness, accompanied by glycaemia level as low as 1.4 mmol/l, began to occur repeatedly, and were stopped with intravenous administration of glucose solution performed by an ambulance team. However, no elevation of insulin of C-peptide was registered. MSCT of the brain did not reveal any lesions.

In May 2019, the patient was admitted to the local facility. Spontaneous hypoglycemia was repeatedly recorded both on fast and post-meal (up to 2 times a day), and therefore, provocative tests were not carried out. The patient's laboratory data during one of the spontaneous hypoglycemic episode (Table 2) corresponded to hypoinsulinemic hypoglycemia. It is important to note that insulin levels were measured exclusively by ROCHE ELECSYS Insulin (RE).

For the prevention of hypoglycemic conditions, additional nutrition with a high content of simple and complex carbohydrates was recommended, with a registered positive effect (the glucose level varied from 3.2 to 7.3 mmol/l). A survey was initiated to find the causes of hypoinsulinemic hypoglycemia. Adrenal insufficiency was excluded – random cortisol 675.9 nmol/l (reference values 171-536), ACTH 26.88 pg/ml

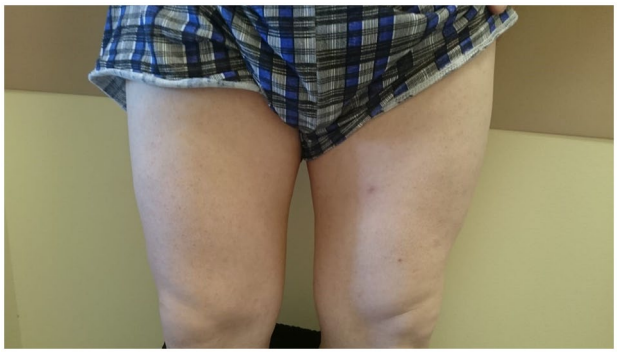

Figure 1. Injection marks on the left thigh skin.

(reference values 7.2-63.3). The blood tests for tumor markers and an oncological search were initiated to exclude the presence of a non-β-cell tumor. However, the levels of chromogranin A, α-fetoprotein, gastrin, free β-human chorionic gonadotropin and cancer embryonic antigen were within the reference values. Contrast-enchanced MSCT of the chest, abdominal cavity and retroperitoneal space, as well as esophagogastroduodenoscopy did not reveal any tumor. It is important to note that, according to the results of MSCT, fluid structures were identified in the right gluteus maximus muscle with a maximum size of 28 × 32 mm. Having discussed these data with the patient, the doctors of the local facility suggested, that the presence of fluid structures is caused by intramuscular injections of vitamin B-complex and non-steroidal anti-inflammatory drugs before hospitalization.

The patient was discharged with recommendations for positron emission tomography (PET) to exclude non-β-cell tumors. In July 2019 PET with 68Ga-DOTA-TATE was performed; however, no neuroendocrine tumors were detected. The patient was recommended to be admitted to a specialized endocrine hospital.

Upon admission to the ERC in July 2020 vital signs were: weight 78 kg, height 1.75 m, BMI 24.9 kg/m^2, blood pressure 140/60 mmHg. During the general examination, attention was drawn to the patient's athletic constitution (given that over the past several years the patient did not do regular strength training). In addition, on the left thigh, we detected skin changes in the form of small dots that resembled injection sites (Figure 1, according to the patient, mosquito bites). The rest of the organs and systems were normal.

The patient denied the presence of concomitant diseases, as well as the intake or administration of any medications. The patient paid attention to disability due to the long-time presence of episodes of hypoglycemia (since 2019, he has been working at home). The family history of the patient showed that the grandfather had type 2 diabetes and received insulin treatment.

Provocative tests were performed in the hospital department to diagnose HGS. During the examination, glycemic control was carried out using a glucometer and a device for real-time continuous glucose monitoring (RT-CGM) (Figure 2).

During the provocative test with mixed meal, hypoglycemia was achieved 2 hours after the food intake. In addition, during the examination period, spontaneous hypoglycemia was repeatedly recorded. After spontaneous hypoglycemia the glucagon test was performed. The patient's laboratory data in the ERC are presented in Tables 3 to 5.

In accordance with the data obtained, the presence of hypoinsulinemic hypoglycemia was confirmed; IGF- and pro-IGF-producing tumors were excluded. Taking into account the skin changes in a patient with hypoinsulinemic hypoglycemia, suspicious with regards to injection sites, long periods of disability, a history of "remission" of attacks for several years, the presence of a relative with diabetes, deliberate administration of insulin analogs was assumed. In this connection, an additional investigation of the same blood samples at the moment of hypoglycemia (at the end of the mixed meal test and before the glucagon test) was carried out using the ABBOTT ARCHITECT Insulin (AA). We obtained the insulin level much more than 3 μU/ml when using the AA kit, as opposed to RE kit. The results of this study supposed the exogenous administration of the insulin preparation. The surreptitious HGS was also confirmed by the data of the test with glucagon (the increment in glycaemia of more than 1.4 mmol/l indicates the presence of hyperinsulinemia) and a low beta-hydroxybutyrate level at the moment of hypoglycemia. Low beta-hydroxybutyrate level at the moment of hypoglycemia is also typical for hyperinsulinemia. The increased GH level in our opinion is due to counter-regulatory response to hypoglycemia.

Thus, Munchausen syndrome was confirmed. Most probably, the patient used his grandfather's insulin. After discussing the results, the patient did not deny the additional administration of insulin preparations. We had a serious conversation about the need to take medications only with doctor's prescription and the potential danger to life and health of independent use. A psychiatrist consulted the patient and diagnosed the mixed anxiety-depressive disorder. The patient was given recommendations for drug treatment and further psychotherapy.

Discussion

We describe the patient with long-term history of HGS. The results of laboratory examination, which revealed hypoinsulinemic hypoglycemia, were suspicious for counter-hormone deficiencies and non-β-cell tumors. As there were no signs for the former possibility and as no tumors could be identified concerning the latter diagnosis, the most probable diagnosis was self-injection of insulin, which was not identified by the first insulin kit test (RE). Taking into account no increase in the levels of insulin and C-peptide, surreptitious oral-hypoglycemic agents intake was excluded. Finally, we carried out additional investigation of the same blood samples at the moment of hypoglycemia using the insulin kit test with high cross-responsiveness with insulin analogs (AA). The results of this study confirmed the exogenous administration of the insulin

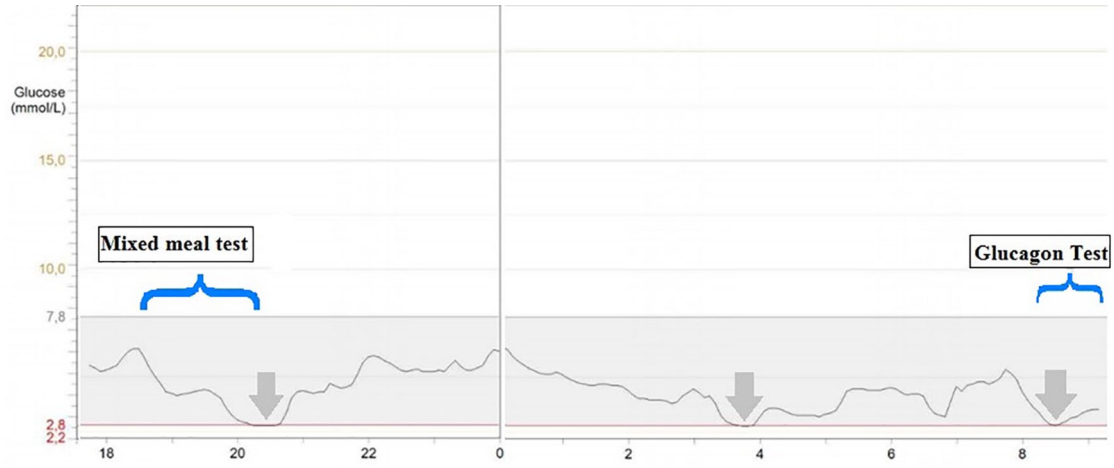

Figure 2. RT-CGM report during the examination in the ERC.
Arrows indicate the episodes of hypoglycemia.

Table 3. Examination Results at the End of A Mixed Meal Test in the ERC.

TEST	VALUE (UNITS)	REFERENCE INTERVAL
Glucose	1.5 mmol/l	3.1-6.1
Insulin (RE)	1.52 μU/ml	2.6-24.9
C-peptide	0.9 ng/ml	1.1-4.4
Insulin (AA)	45 μU/ml	2.6-24.9
Proinsulin	4.82 pmol/l	<5
β-hydroxybutyrate	0.1 mmol/l	<0,6
GH	9.22 ng/ml	0.02-1.23
IGF1	164.4 ng/ml	82-283
IGF2	362.4 ng/ml	442-1049
IGF2:IGF1	2.2	<10
pro-IGF2	1529.5 pg/ml	84.2-3370.9

Table 4. Examination Results At the Beginning of the Glucagon Test in the ERC.

TEST	VALUE (UNITS)	REFERENCE INTERVAL
Glucose	1.86 mmol/l	3.1-6.1
Insulin (RE)	0.2 μU/ml	2.6-24.9
C-peptide	0.268 ng/ml	1.1-4.4
Insulin (AA)	53 μU/ml	2.6-24.9

preparation. Thus, the use of an alternative insulin kit test was critical to diagnose the hyperinsulinic pattern of hypoglycemia.

Presented clinical case has some features:

- Taking into account the manifestation (after long «remission» period) of hypoglycemic attacks in the summer of 2018, when the patient began short-term training in the gym, insulin injections most probably were performed by him for anabolic purposes (similar case was described in the literature[21]). We cannot exclude, that he injected the drug intramuscularly, and that caused the formation of fluidic structures (identified according to the data of MSCT).
- Taking into account the results of tests from 2008 (according to the patient, the insulin level at the moment of hypoglycemia was elevated), we assumed that previous hypoglycemia episodes were caused by administration of human insulin or oral antihyperglycemic drugs.
- In addition, we received ambiguous results of the mixed meal test (lack of C-peptide suppression in concordance with Endocrine Society[22]). We believe that these results are due to the longer period of half-life of C-peptide comparing with insulin.[23] Thus, even in the absence of appropriate C-peptide suppression, exogenous insulin injection cannot be excluded.

Table 5. Examination Results During A Glucagon Test in the ERC.

TEST	VALUE (UNITS)
Glucose (0 min)	1.86 mmol/l
Glucose (+3min)	2.3 mmol/l
Glucose (+5 min)	2.6 mmol/l
Glucose (+10 min)	3.3 mmol/l
Glucose (+15 min)	3.8 mmol/l
Glucose (+20 min)	3.6 mmol/l
Glucose (+30 min)	2.3 mmol/l

Conclusion

1. This clinical case clearly shows the need for vigilance in relation to deliberate administration of antihyperglycemic

drugs in all hypoglycemia cases, and attention to anamnesis and examination data. Timely diagnosis of surreptitious HGS will prevent multiple imaging studies aimed to find the source of insulin hypersecretion, including costly, invasive and possessing radiation load ones, and provide appropriate psychiatric/psychological care;

2. Taking into account the variability of cross-reactivity of different kits with insulin analogs, it is possible to obtain false-negative results in cases of its surreptitious administration. In this connection, the patient is assumed to have hypoinsulinemic hypoglycemia. Thus, laboratory service takes the key role in diagnostics of exogenous insulin analogs injection and should be aware of specificity of used insulin kit for correct interpretation of results.
3. Surreptitious injection of insulin analogs is suspected in cases of the presence of relatives with type 2 diabetes, injection marks on the body, variability of symptoms. If insulin kit test with low cross-reactivity with insulin analogs (Table 1) is used, the hypoinsulinemic hypoglycemia (insulin <3 μU/ml, C-peptide <0.6 ng/ml) will be suspected. In these cases, it is necessary to determine insulin levels using insulin kit test with high cross-responsiveness with insulin analogs in the same blood sample. If insulin kit test with high cross-reactivity with insulin analogs is used, the high level of insulin (>3 μU/ml) and suppression of C-peptide (<0.6 ng/ml) will be revealed.

Patient consent confirmation statement

The written informed consent to the publication of this article was obtained from the patient.

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